REMARKS

The title of the invention has been amended to more clearly indicate the invention to which the claims are directed.

The Specification has been amended to correct the claim to priority and to correct a typographical error. In addition, the SEQ ID NO. for the amino acid sequence disclosed on page 25, line 26 has been added.

Claims 81 and 103 have been amended to indicate that the number of amino acid substitution does not exceed 60. Support for this amendment can be found in the Specification on page 21, line 5.

New claims 105-110 have been added. Support for these claims can be found throughout the Specification, but in particular on pages 8, 13 (lines 6-26), page 17 (lines 19-24), page 28 (lines 5-18) and Example 1.

No new matter has been added.

Objections

The Examiner has objected to the Specification for failing to disclose a SEQ ID NO. for the amino acid sequence disclosed on page 25, line 26. Applicants have amended the Specification to indicate the proper SEQ ID No. In addition, Applicants submit a substitute Sequence Listing which contains the amino acid sequence of page 25, line 26 as well as a CRF disk containing an electronic copy of the Sequence Listing. The paper copy of the Sequence Listing is identical to the electronic copy found on the CRF.

Applicants have also corrected the typographical error relating to the term "Fcγ" and have amended the first line of the Specification to properly claim benefit of priority to earlier applications.

Lastly, Applicants have amended the title to more clearly describe the invention.

New Matter

Rejections Under 35 USC § 112

The Examiner has rejected claims 81 - 83 and 103 as containing subject matter which was not described in the Specification, i.e. new matter. Applicants respectfully traverse.

Applicants note that throughout the Specification, the idea of modifying a GDF-8 analogue by inserting more than one foreign T-cell epitopes is presented, see for example, on page 13, lines 15-19. More specifically, on page 28, lines 21-27, the Specification clearly states that modification **in at least one of**, a particular group of subsequences of C-terminal GDF-8 will result in suitable immunogenic molecules. This concept is repeated in the passage beginning on page 28, line 33 to page 29, line 7. In view of this, Applicants respectfully request reconsideration and removal of the rejection.

Enablement

The Examiner has rejected claims 81-83 and 103-104 for lack of enablement. The Examiner acknowledges that there is enablement for a GDF-8 analogue derived from animal GDF-8 polypeptide where the analogue has been modified by substituting at least one first amino acid in SEQ ID NO. 12 with at least one second amino acid sequence comprising a foreign T_H epitope where the T_H epitope is *Tetanus toxoid* epitope and where the first amino acid sequence is from residues 1-12, 18-30, 42-51, 82-86 and 105-109. The Examiner contends that there is no enablement for *any* GDF-8 analogue derived from animal GDF-8 polypeptide where at least one first amino acid in SEQ ID NO. 12 has been substituted with at least one second amino acid comprising any foreign T_H

epitope. The Examiner contends that undue experimentation would be required in order to practice the invention as claimed.

The Examiner reiterates that only a GDF-8 analogue where the T_H epitope is the *Tetanus toxoid* epitope is enabled. He states that the Applicants have not taught how to make and/or use *any* GDF-8 analogue comprising *any* foreign T_H epitope to down regulate GDF-8 to increase muscle mass.

The Examiner embarks on a lengthy discussion of how single amino acid changes in an antigen can effectively abolish antigen binding, citing to Colman et al., Abaza et al. and Lederman et al. This lengthy discussion is not repeated here but can be found on pages 4-5 of the Office Action. The Examiner concludes that, "a skilled artisan would require guidance, such as information regarding the specific epitope recognition of the antibodies successfully used in the instant invention in a manner reasonably commensurate with the scope of the claims." The Examiner follows this by saying that it would require undue experimentation to practice the claimed invention and that "since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them." Applicants respectfully traverse.

Applicants first point out that claims 81 and 103 have been amended to require that the GDF-8 analogue comprises SEQ ID NO. 11 or 12. As such, the claims are limited to GDF-8 analogues having these sequences and are not directed to any GDF-8 analogue. In addition, the amended claims also ensure that the total number of amino acid changes in SEQ ID NO. 11 and 12 does not exceed 60. This puts an upper limit to the number of possible variants of SEQ ID NO. 11 or 12.

It appears that the Examiner's view point is that the application does not enable use of any T_H epitope. It only makes sense, however, to define T_H epitopes functionally because there is no structural definition of such epitopes. This can be compared to, for example, patents that mention "cytokines," "lymphokines," and "hormones" in patent claims. These terms all refer to functionality and not to structure. It is therefore difficult to understand why a "T_H epitope" should be difficult to understand for a skilled immunologist. All persons skilled in immunology would know that a T_H epitope is a short peptide that bines a MHC Class II molecule and is recognized by T_H cells. This definition appears in the Specification.

The *Tetanus toxoid* epitopes P2 and P30 are exemplary. The skilled immunologist would find no sound scientific reasoning to indicate that other foreign T_H epitopes would be incapable of providing the same effect. While it is true that the Specification mentions that promiscuous foreign T_H epitopes are relatively rare, the claims are **not** limited to promiscuous epitopes. Non-promiscuous foreign T_H epitopes are quite abundant. The ultimate advantage of using promiscuous epitopes is that a single vaccine molecule will be effective in a large proportion of a population. The claimed invention, however, does not require that such broad-spect red molecules are used. It only states that using such molecules is an alternative to immunizing patients with a combination of several molecules that together cover a suitable proportion of a population. In addition, the current definition of the term "variant" ensures that sufficient GDF-8 material is preserved in the analogues of the invention so that cross-reacting antibodies will be produced by the immunized animal.

While the references by Colman, Abaza and Lederman discuss single amino acid changes that have the potential to abolish antibody binding, these references relate to binding by monoclonal antibodies as opposed to polyclonal antibody binding. Here, the references demonstrate that *single* epitopes are destroyed by point mutations. A vaccine molecule of the present invention, however,

induces a polyclonal response directed to several epitopes on the molecule. While it is possible that one of the epitopes found in the unmodified GDF-8 molecule could be lost, it is inconceivable that all epitopes should be lost because some epitopes are linear. Consequently, it is a fact that epitope prediction is unnecessary in order to work the present invention. Even in the case of the maximum number of 60 amino acid changes, there are still 49 amino acids left from SEQ ID NO. 11 and 12. Hence, at the very least the linear epitopes in these regions are left unaltered and antibodies against these epitopes would cross-react with the native protein having SEQ ID NO. 11 or 12. The claims do not indicate that all epitopes of GDF-8 should be preserved.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Written Description

The Examiner has rejected claims 81-83, 103 and 104 as lacking written description. The Examiner acknowledges that written description exists for a GDF-8 analogue derived from animal GDF-8 polypeptide having at least one first amino acid from SEQ ID NO. 12 substituted with at least one second amino acid comprising a foreign T_H epitope, specifically a *Tetanus toxoid* epitope. He contends, however, that there is no written description for *any* GDF-8 analogue derived from animal GDF-8 polypeptide where at least one first amino acid sequence and SEQ ID NO. 12 has been substituted with a sequence comprising *any* foreign T_H epitope. The Examiner states that "no structural or specific functional characteristics of such an analogue is provided." He also notes that while a number of species have been disclosed, the skilled artisan cannot envision all of the contemplated amino acid sequence possibility recited in the instant claims. Applicants respectfully traverse.

Applicants again point out that the claims have been amended to require a GDF-8 analogue comprising SEQ ID NO. 11 or 12. Consequently, the claims do not encompass *any* GDF-8 analogue.

As discussed above, it only makes sense to define T_H epitopes functionally because there is no general structural definition of such epitopes. Applicants have included such a functional description of a T_H epitope. See, for example, page 13, lines 7-26 and page 24, lines 15 to page 25, line 33. Here, while Applicants have not specifically included the epitope sequence in the sequence listing, Applicants have provided a significant number of examples of appropriate T_H epitopes. It is not required to list each and every example. In addition, the vast majority of these epitopes are known to those skilled in the art and are recognized in the absence of a sequence listing. Therefore, Applicants respectfully request reconsideration and removal of the rejection.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 81-83 and 103-104 as being obvious over USP 6,369,201 ('201) or USP 6,607,884 ('884). The Examiner contends that USP '201 teaches a GDF-8 analogue derived from animal and linked to an immunological carrier, and where SEQ ID NO.: 2 in the '201 patent is 100% identical to SEQ ID NO. 12 of the instant application. The Examiner further contends that USP '201 teaches that the term "myostatin immunogen" includes a polypeptide of myostatin, analogue and modification by substitution so that a substantial fraction of myostatin B cell epitopes are preserved and do not effect the ability of the analogue to induce an immunological response. The Examiner alleges that USP '201 indicates that modification includes duplication of at least myostatin B cell epitope and that in order to facilitate breaking of auto tolerance that myostatin may be modified with a foreign T_H epitope such as *Tetanus toxoid* epitope. The Examiner contends

that USP '884 teaches GDF-8 analogue derived from animal and myostatin immunoconjugate comprising at least one myostatin analogue. The Examiner notes that USP '884 teaches SEQ ID NO.: 21 which is 100% identical to SEQ ID NO.: 12 of the instant application. USP '884, according to the Examiner, teaches that GDF-8 analogue can be a minor modification, including deletion or substitution, which has substantially equivalent activity and that it is well known in the art that in order to increase immunogenicity, GDF-8 analogue can be modified with foreign T_H epitope, such as *Tetanus toxoid* epitope.

The Examiner acknowledges that neither USP '201 or USP '884 explicitly teaches the particular modification of myostatin where the molecule has been modified so that at least one foreign T_H epitope moiety is introduced at amino acid from 18-41 of myostatin SEQ ID NO.: 12.

The Examiner supports his contention of obviousness by stating that the Specification disclosed the existence of various methods of modifying a peptide self-antigen in order to obtain breaking of autotolerance, including introducing at least one foreign T cell epitope such as *Tetanus toxoid.* He further notes that the Specification discloses setting up an effective standard screen for modified GDF-8 molecules, which fulfills the minimum requirements for immunological reactivity. From this the Examiner concludes that the Applicants acknowledge that it is within the skill of the art to identify the exact position for substitution with T_H epitope in myostatin molecules in order to increase immunogenisity of GDF-8 analogues and facilitating the breaking of autotolerance. The Examiner further concludes that it would have been obvious to a skilled artisan to apply the teaching of the facts disclosed in the Specification to those of USP '201 or USP '884 to obtain the claimed GDF-8 analogues derived from animal GDF-8 polypeptide where the analogue has been modified by substituting at least one first amino acid in SEQ ID NO.: 12 with at least one second amino acid sequence comprising a foreign T_H epitope wherein said first amino acid sequences from residues 18-

41. The Examiner contends that the skilled artisan would have been motivated to do so because it is well known in the art that modifying a peptide self-antigen by introducing at least one foreign T cell epitope will facilitate breaking of autotolerance and that it is not difficult to set up an effective standard screen for modified GDF-8 molecules which fulfills the minimum requirements. The Examiner states, "said specific position of modified GDF-8 analogue can be applied to GDF-8 analogue taught by USP '201 or USP '884." The Examiner supports his argument by citing to *In Re Aller*, 105 USPQ 233; 235. Applicants respectfully traverse.

The current limitations of the claims, i.e. the positions in SEQ ID NO.: 11 or 12 to be modified and the maximally allowed 60 amino acid changes **cannot** be derived from the prior art on record.

The Examiner has relied on the "known fact" (pages 16 and 51 of the Specification) to reject the claims for being obvious. Applicants respectfully point out, however, that numerous patents relating to chemical compounds (as an example) have been granted, even though the claimed compounds have been identified by means of standard screening procedures. A standard protocol for screening compounds, however, does **not** per se render a novel compound obvious.

In addition, the holding of *In Re Aller* refers to claims wherein the Applicants specified lower temperatures and higher sulfuric acid concentrations than those found in the cited references. Here, primary Examiner held that the conditions resulted simply from experimentally varying the optimum reaction conditions and the Board of Appeals affirmed this finding. The situation in the present application is significantly different from that of *In Re Aller*. Here, particular regions of a polypeptide have been found to be superiorly suited for performing particular modifications. That is, the skilled artisan would **not** been able to predict precisely which variant, if any, would prove effective and this is not analogous to optimizing temperatures and concentrations as was the case

with *In Re Aller*. As a consequence, there is no *prima facie* case of obviousness and Applicants respectfully request reconsideration and removal of the rejection.

In view of the above remarks, all of the claims remaining in the case are submitted as defining non-obvious, patentable subject matter.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), the Applicant respectfully petitions for a two (2) month extension of time for filing a response in connection with the present application and the required fee of $420.00 is to be charged to Deposit Account 02-2448.

Conclusion

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: May 31, 2005
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BIRCH, STEWART, KOLASCH & BIRCH, LLP

(Signature)

5/31/05
(Date of Signature)

LRS/SWG/sbp
4614-011IP
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Respectfully submitted,

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